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ORIGINAL ARTICLE

Multifaceted impairments in impulsivity and brain structural abnormalities in opioid dependence and abstinence

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Background. Chronic opioid exposure, as a treatment for a variety of disorders or as drug of misuse, is common worldwide, but behavioural and brain abnormalities remain under-investigated. Only a small percentage of patients who receive methadone maintenance treatment (MMT) for previous heroin misuse eventually achieve abstinence and studies on such patients are rare.

Method. The Cambridge Neuropsychological Test Automated Battery and T_1 weighted magnetic resonance imaging (MRI) were used to study a cohort of 122 male individuals: a clinically stable opioid-dependent patient group receiving MMT ($n = 48$), an abstinent previously MMT maintained group (ABS) ($n = 24$) and healthy controls ($n = 50$).

Results. Stable MMT participants deliberated longer and placed higher bets earlier in the Cambridge Gambling Task (CGT) and showed impaired strategic planning compared with healthy controls. In contrast, ABS participants showed impairment in choosing the least likely outcome, delay aversion and risk adjustment on the CGT, and exhibited non-planning impulsivity compared with controls. MMT patients had widespread grey matter reductions in the orbitomedial prefrontal cortex, caudate, putamen and globus pallidus. In contrast, ABS participants showed midbrain–thalamic grey matter reductions. A higher methadone dose at the time of scanning was associated with a smaller globus pallidus in the MMT group.

Conclusions. Our findings support an interpretation of heightened impulsivity in patients receiving MMT. Widespread structural brain abnormalities in the MMT group and reduced brain structural abnormality with abstinence suggest benefit of cessation of methadone intake. We suggest that a longitudinal study is required to determine whether abstinence improves abnormalities, or patients who achieve abstinence have reduced abnormalities before methadone cessation.

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Key words: Abstinence, impulsivity, opioid dependence, structural magnetic resonance imaging.

Introduction

Worldwide, long-term exposure to opioids such as morphine, codeine, heroin and methadone is common, both in the substance misuse and other clinical populations. Chronic use of opioids leads to long-lasting changes, including tolerance, sensitization and physical dependence (Trujillo, 2002). One of the most common opioid drugs to be misused is heroin, which is also prescribed in the UK as 'diamorphine' as an analgesic (Strang *et al.* 2012). For those seeking treatment after developing dependence following repeated exposure to illicit heroin, methadone maintenance treatment (MMT) is the most commonly offered therapeutic intervention. In Scotland alone, 30 000 patients receive MMT as part of a 'harm reduction programme' to reduce or cease heroin use, diminish associated criminality, and reduce the risk of blood-borne virus infection (McKeganey *et al.* 2006). However, an MMT programme is associated with low rates of sustained abstinence with as few as 17–28% of those dependent on MMT achieving abstinence (The Scottish Government, 2010). One of the core features of opioid dependence is the dysregulation of dopaminergic neurotransmission, including decreased dopamine receptor availability and release (Gradin *et al.* 2014), associated with functional impairments in frontal brain regions innervated by dopamine. However, it is not known whether the effects of opioids could lead mechanistically to long-lasting changes, or could be reversible following a period of abstinence (Ersche *et al.* 2005; Baldacchino *et al.* 2015).

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Chronic misuse of drugs appears to be associated with a variety of cognitive abnormalities. Such deficits may have important clinical consequences: e.g. increasing drug-seeking, presumably due to a failure of impulse control and impaired engagement in therapeutic programmes, with increased rates of relapse following treatment (Rogers & Robbins, 2001). In comparison with work on stimulants and cannabis, there has been less research on cognitive impairments associated with opioid dependence (Baldacchino *et al.* 2012). Opioid-dependent subjects discounted the value of delayed money rewards more than non-drug-using participants, and discounted the value of delayed heroin more than delayed money (Madden *et al.* 1997). Whilst some researchers concluded that opioid misuse is not associated with frontal lobe impairments, others reported that it is associated with a broad range of deficits such as attentional control, planning and spatial working memory (Ornstein *et al.* 2000). More recently, 'reflection impulsivity', the extent to which subjects sample information before responding, has been reported as decreased in currently opioid-dependent and former substance misusers (Clark *et al.* 2006). A variety of cognitive deficits associated with opioid misuse has, therefore, been reported, ranging from general deficits, to selective memory impairment, increased discounting and impulsivity, to no prefrontal-linked cognitive impairments. Importantly, these studies have revealed significant overlaps in candidate markers of impulsivity (Dalley *et al.* 2011; Robbins *et al.* 2012).

A post-mortem study reported an increased prevalence of ischaemic brain lesions in the globus pallidus in opioid-dependent individuals (Andersen & Skullerud, 1999). Structural magnetic resonance imaging (MRI) studies of human opioid-dependent populations have revealed significant grey matter reductions in the prefrontal and temporal cortices (Lyoo *et al.* 2006; Liu *et al.* 2009; Yuan *et al.* 2009) and increased white matter hyper-intensities, mainly in frontal areas (Lyoo *et al.* 2004). Indeed, overall results show that the neuroanatomical impairments are located in neural networks linked to executive and attentional function, such as the dorsolateral prefrontal cortex, anterior cingulate cortex and medio-temporal cortices. Abstinent previously heroin-dependent individuals have shown, after 3 days of abstinence, significant grey matter reductions in the left frontal gyrus and cingulate gyrus. However, after 1 month of abstinence there were no significant differences between patients and controls in any structural brain region (Wang *et al.* 2011).

Previous studies investigating the chronic effects of opioid use either due to heroin misuse or as part of MTT have largely focused on the evaluation of cognitive impulsivity and non-planning impulsivity using Barratt's Impulsivity Scale (Patton *et al.* 1995; Ersche *et al.* 2005; Baldacchino *et al.* 2015). The prefrontal cortex may play a key role in processing such information (Rogers *et al.* 1999). However, to our knowledge, only one study has reported significant orbitofrontal structural abnormalities associated with heroin and methadone use (Ersche *et al.* 2006).

The aim of this study was to test the following hypotheses:

(i) Behavioural impairment in cognitive impulsivity and non-planning impulsivity are related to different stages of treatment (stable MMT use *v.* abstinent).

(ii) Stable MMT patients exhibit more reductions in grey matter volume in a *priori* regions of interest, such as the prefrontal cortex and basal ganglia, because these regions have been linked to impulsivity and reported as abnormal in structure in opioid misuse (Robbins *et al.* 2012), relative to controls and abstinent patients. MMT patients may be most vulnerable to the effects of current opioid exposure associated with cognitive impulsivity and non-planning impulsivity (Robbins *et al.* 2012). We therefore predicted that behavioural measures of impulsivity correlate with brain structure measures.

Method

Participants

Study approval was granted by the East of Scotland, the Lothian and Glasgow Research Ethics Committees and written informed consent obtained from all participants. National Health Service (NHS) Scotland Research Governance approvals were provided by the NHS Fife Research and Development Department. The University of Dundee was the sponsor for this study.

A total of 122 male individuals were enrolled in the study. They underwent detailed clinical screening assessed by a clinician (A.B. or S.G.) that included the collection of sociodemographic information, and semi-structured interviews to ascertain detailed histories of drug and alcohol use and opioid-dependence status (Marsden *et al.* 1998). Mental health status and history were assessed using the Mini International Neuropsychiatric Interview (MINI Plus, version 5.0; Sheehan *et al.* 1998). Current and pre-morbid intelligence was estimated using the Wechsler Abbreviated Scale of Intelligence and National Adult Reading Test (NART) (Nelson & Willison, 1991; Woerner & Overstreet, 1999). The Fagerström Test for Nicotine Dependence (Fagerstrom & Schneider, 1989) was also used.

Case records from the addiction, psychiatric and general practitioners' services helped in the identification of overdose episodes, confirmed the absence of a

history of epilepsy and other neurological phenomena, hepatitis B, C and HIV status and diagnoses of personality disorders (e.g. borderline). These records also allowed us to validate medical and psychiatric histories, substance misuse career timelines and quantify current drug and alcohol use. Exclusion criteria were past or current histories of psychotic disorder, post-traumatic stress disorder, neurological and neurodevelopmental disorders, head injury, confirmed history of non-fatal overdose episodes and co-occurring benzodiazepine, stimulant and alcohol dependence, and antisocial and borderline personality disorder.

The methadone group ($n = 48$) had a diagnosis of Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) opioid dependence and were engaged in a methadone maintenance programme (MMT) with objective confirmation of the absence of illicit drug use for more than 6 months. The previously dependent opioid (abstinent; ABS) group ($n = 24$) had a history of chronic opioid use with an abstinence duration exceeding 6 weeks. As patients were either stably maintained on methadone or were stably abstinent, no acute intoxication or withdrawal effects were observed. A representative subset of these volunteers took part in stages 2 and 3. Both MMT and ABS groups had been taking between 30 and 120 mg of methadone daily on an MMT programme and presented with more than 3 years of continuous daily illicit heroin use. The two groups were matched by lifetime drug use and methadone doses [initial titration of methadone dose (ITMD), current methadone treatment dose (CMTD) and/or last stable methadone dose (LSMD)]. The ITMD included the initial titration dose of methadone that each patient received, defined as the dose of methadone required to reduce heroin withdrawal symptoms at the commencement of MMT and was between 10 and 30 mg daily, depending on objective evidence of opioid withdrawal symptoms. Ongoing abstinence from illicit drug use was confirmed just prior to both neuropsychological testing, and scanning, using an onsite multidrug urine test (Armbruster & Krolak, 1992). Some participants withdrew from scanning and from neuropsychological assessment because they were not contactable or they were not able to take part. Details of participants included in the analysis are presented in Table 1. Fig. 1 describes the cohorts who participated in the stages of the study as described below.

Stage 1 – behavioural outcomes

Each participant was assessed using the standardized Cambridge Neuropsychological Test Automated Battery (CANTAB; http://www.cambridgecognition.com). Executive functions were assessed using the Cambridge Gambling Task (CGT) and Stockings of Cambridge (SOC) tests. These tasks assessed cognitive impulsivity and non-planning impulsivity, respectively (Patton *et al.* 1995; Ersche *et al.* 2005; Baldacchino *et al.* 2015).

Statistical analysis of the behavioural outcomes

Data meeting assumptions of normality and homogeneity of variance were analysed using analysis of variance (ANOVA) and analysis of covariance (ANCOVA). All other data were compared using appropriate non-parametric tests (e.g. Kruskal–Wallis and Mann–Whitney tests). ANOVA was used to test for group differences. To control for family-wise error, we used *post-hoc* Bonferroni-corrected pairwise comparisons. After correction, results with $p < 0.05$ were considered significant. ANOVA was used to test for group differences. Effect sizes were calculated as Cohen's d statistics and analyses conducted using SPSS v. 20 (SPSS Inc., USA).

Stage 2 – neuroimaging

Scanning

Data were acquired with a Siemens 3 T Tim Trio at the Clinical Research Centre, Ninewells Hospital and Medical School, Dundee, UK. 'Structural' T_1 weighted images were acquired with a voxel size $0.8 \times 0.8 \times 1.0$ mm^3 with whole brain coverage, repetition time (TR) = 1.9 s and echo time (TE) = 2.64 ms and reported by a consultant radiologist for incidental findings.

Image analyses

Voxel-based morphometry was done using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). For pre-processing, T_1 weighted images for each participant were segmented into grey and white matter probability maps, spatially normalized with modulation to preserve the total amount of grey matter and smoothed with an 8 mm Gaussian kernel (Ashburner & Friston, 2005). We used t tests to test the null hypothesis of no difference between MMT patients and controls.

The threshold of significance was defined as $p < 0.05$ at a whole-brain corrected level using a customized version of a popular Monte Carlo technique (Slotnick *et al.* 2003) (http://www2.bc.edu/~slotnics/scripts.htm). Brain regions were identified by converting Montreal Neurological Institute coordinates into Talairach coordinates using the Yale conversion calculation (http://bioimagesuite.yale.edu/mni2tal/index.aspx) and inspection of the Talairach Atlas (Talairach & Tournoux, 1988).

Table 1. *Demographic and clinical characteristics*

	Stage 1				Stage 2				Stage 3			
	MMT	ABS	HC	Significance	MMT	ABS	HC	Significance	MMT	ABS	HC	Significance
n	48	25	50		33	15	23		18	15	23	
Age, years	30.2 (4.7)	36.6 (3.9)	28.0 (7.0)	ABS > MMT*	33.9 (4.2)	37.0 (3.7)	30.8 (6.9)	N.S.	33.6 (4.8)	37.0 (3.7)	30.8 (6.9)	N.S.
NART	103.0 (9.4)	111.3 (2.1)	117.9 (6.0)	MMT < HC***	114.6 (5.2)	109.7 (7.9)	117.0 (7.0)	ABS < HC*	113.0 (4.8)	109.7 (7.9)	117.0 (7.0)	ABS < HC*
ITMD, mg/day					50.0 (19.0)				49.8 (19.0)			N.S.
SMD, mg/day	66.6 (21.5)	79.0 (36.0)	–	N.S.	74.7 (18.8)	79.0 (36.0)	–	N.S.	71.1 (21.2	79.0 (36.0)	–	N.S.
Age of first use of heroin, years	19.1 (3.7)	19.1 (5.7)	–	N.S.	16.1 (3.5)	14.1 (3.6)	–	N.S.	16.1 (3.5)	14.1 (3.6)	–	N.S.
Duration of opioid use, years	9.2 (19.6)	3.8 (11.2)	–	N.S.	9.1 (19.6)	3.8 (11.2)	–	N.S.	6.2 (21.6)	3.8 (11.2)	–	N.S.
Age of first injecting opioids, years	18.1 (8.0)	22.3 (7.0)	–	N.S.	18.1 (8.0)	22.3 (7.0)	–	N.S.	18.1 (8.0)	22.3 (7.0)	–	N.S.
Fagerström total score	5.16 (6.4)	9.2 (14.1)	–	N.S.	3.8 (1.9)	8.1 (13.0)	–	N.S.	3.6 (1.9)	8.1 (13.0)	–	N.S.
Duration of abstinence, days	–	–	–	–	–	160.6 (66.7)	–	–	–	155.4 (68.7)	–	N.S.

Data are given as mean (standard deviation).

MMT, Methadone maintenance group; ABS, abstinent group; HC, healthy control group; N.S., not significant; NART, National Adult Reading Test; ITMD, initial methadone titration dose; SMD, stable methadone dose.

* $p < 0.05$, *** $p < 0.001$.

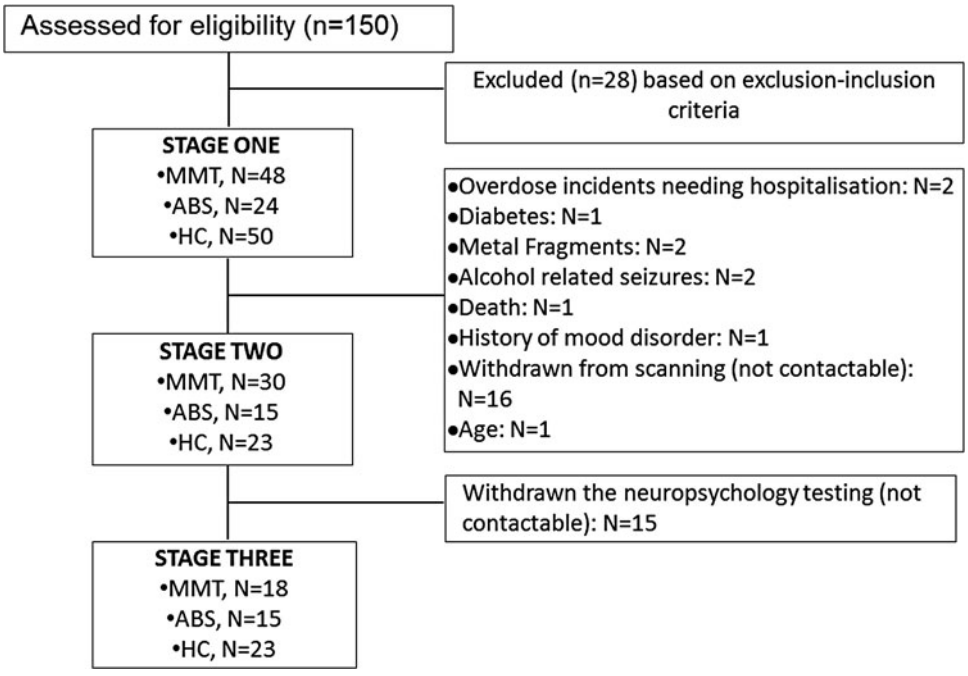

Fig. 1. Flowchart of study stages and participants. MMT, Methadone maintenance treatment group; ABS, abstinent group; HC, healthy controls.

Stage 3 – behaviour and neuroimaging and correlations with opioid exposure

Correlation analyses were similarly used to test null hypotheses of no relationship between grey matter indices and measures of opioid exposure: ITMD and CMTD. Correlation analyses were also used to test null hypotheses of no relationship between grey matter abnormalities and CGT or SOC behavioural measures.

Statistical analysis for treatment outcome

An exploratory analysis to investigate potential predictors of outcome was also done. Logistic regression with 6-fold cross-validation was used to generate an unbiased prediction of treatment outcome (MMT *v.* ABS) in the experimental groups using the following predictors: frequency use, withdrawal exposure and treatment. We were interested in particular in two measures: (1) ITMD and (2) stable methadone dose (SMD) for the MMT group and the LSMD for the ABS group. Analyses were conducted using SPSS for Windows v. 20 (SPSS Inc., USA).

Results

Participants

MMT and ABS groups were matched for clinical characteristics: SMD, age of first use of heroin, years of opioid use, age of first injecting opioids and Fagerström total score in the first stage of the study. The ABS group were on average older than the MMT group ($p < 0.05$) and the MMT group had lower intelligence quotient scores than the healthy control group ($p < 0.001$). In the second and third stages, the ABS group differed significantly in NART scores from the healthy control group ($p < 0.05$) but the clinical characteristics remained matched ($p > 0.05$). Table 1 shows the demographic and the substance use data of the participants.

Behavioural results

Significant decision-making abnormalities for the MMT and ABS groups relative to the control group were identified for cognitive impulsivity (CGT) ($p < 0.01$) and non-planning impulsivity (SOC) ($p < 0.01$) as summarized in Table 2.

Neuroimaging results

As shown in Fig. 2, significant reductions in grey matter probability were present in the MMT group relative to controls: medial-orbital (18, 54, 0) cortices, bilateral caudate (18, 12, 12; −18, 12, 12), bilateral globus pallidus (10, 10, 2; −10, 10, 2), nucleus accumbens (−6, 10, 10), anterior cingulate (−1, 34, 16) and bilateral insula (34, −6, 16; −38, −4, −0). Significant reductions in grey matter were present in the ABS group relative to controls: thalamus (−2, −6, 10) and midbrain (2, 30, 36). This is summarized in Table 3. In the prefrontal cortex, the region of interest was centred on −2, 34, 18.

Table 2. *Between-group comparisons of the neuropsychological domains*

Cognitive test	MMT ($n = 48$)	ABS ($n = 25$)	HC ($n = 50$)	Significance	Effect size	Worse
Cognitive impulsivity (CGT)						
Quality of decision making	0.90 (0.08)	0.85 (0.13)	0.95 (0.05)	ABS < HC***, ABS < MMT***	0.124	↓ MMT↓ ABS
Deliberation time, ms	3247.6 (1520.7)	2936.2 (822.9)	2345.1 (900.0)	MMT > HC**	0.062	↓ MMT
Risk taking	0.6 (0.02)	0.6 (0.03)	0.6 (0.02)	N.S.	0.03	
Overall proportion of bet	0.60 (0.12)	0.55 (0.10)	0.58 (0.10)	N.S.	0.04	
Delay aversion	0.28 (0.17)	0.34 (0.10)	0.23 (0.13)	ABS > HC**	0.07	↓ ABS
Risk adjustment	0.91 (0.75)	0.79 (0.83)	1.50 (0.84)	MMT < HC**, ABS < HC***	0.06	↓ MMT↓ ABS
Non-planning impulsivity (SOC)						
Problems solved in minimum moves	8.4 (1.8)	7.8 (1.5)	9.2 (1.8)	MMT < HC**, ABS < HC**	0.095	↓ MMT↓ ABS
Problems solved in five moves	2.0 (0.2)	1.8 (0.2)	2.7 (0.2)	MMT < HC**, ABS < HC**	0.12	↓ MMT↓ ABS
Mean initial thinking time five moves	6.8 (0.2)	7.1 (0.3)	6.2 (0.2)	MMT < HC**, ABS < HC**	0.088	↓ MMT↓ ABS
Mean subsequent thinking time five moves	1475.0 (334.6)	1735.8 (413.4)	441.5 (340.5)	MMT < HC**, ABS < HC**	0.09	↓ MMT↓ ABS

Data are given as mean (standard deviation).

MMT, Methadone maintenance group; ABS, abstinent group; HC, healthy control group; CGT, Cambridge Gambling Task; ↓, worse; N.S., not significant; SOC, Stockings of Cambridge.

** $p < 0.01$, *** $p < 0.001$.

The MMT group had significantly reduced grey matter probability ($p < 0.001$) in comparison with controls.

Fig. 3 shows that current SMD for the MMT group correlated negatively with bilateral globus pallidus, grey matter probability (20, 2, 6; −20, 4, 6). Increased CGT risk adjustment was associated in the MMT group with bilateral globus pallidus grey matter reductions (20, −4, 6; −24, −6, 10) and increased CGT risk taking was associated with significantly decreased grey matter in the orbitofrontal and inferior medial prefrontal cortices (10, 62, 8; 10, 48, −20) in the MMT group. Increased mean subsequent moves in the SOC were correlated with grey matter reductions in the rostromedial prefrontal cortex (10, 26, −16) in MMT patients, which also correlated with longer times to solve complex problems (such as '5-moves').

In Fig. 4 the LSMD for the ABS group correlated negatively with bilateral: bed nucleus of stria terminalis (BNST) (20, 18, −14; −14, 18, −14), midbrain (−2, −22, 14) and thalamus (−6, −18, 0) grey matter probability. Greater delay aversion on the CGT in the ABS group was associated with periaqueductal grey matter reductions (8, −26, 2). Increased mean subsequent moves of the SOC correlated negatively with grey matter probability in the putamen (−28, 16, 2) and bilateral BNST (24, 18, −24; −22, 16, −24) in ABS patients.

Summary of the neuroimaging and behavioural results

Regions of grey matter reduction in the MMT and ABS participants where the variance in grey matter probability was significantly explained by SMD and LSMD and CGT and SOC behavioural measures are summarized in Table 4 and Fig. 5.

Predictions of treatment outcome

Using logistic regression with cross-validation (within study replication), SMD and LSMD predicted treatment status at the time of the present study (being on MMT treatment *v.* abstinence) with 92% accuracy (98% sensitivity and 72% specificity). In addition, ITMD, which reflected extent of heroin use prior to commencing MMT, predicted treatment status at the time of the present study with 86.2% accuracy (85.7% sensitivity and 86.2% specificity). This indicates that in both ITMD, when commencing MMT, and SMD or LSMD were significant predictors for much later treatment outcomes (Table 5).

Discussion

This study tested the hypotheses that both behavioural and structural grey matter changes were related to

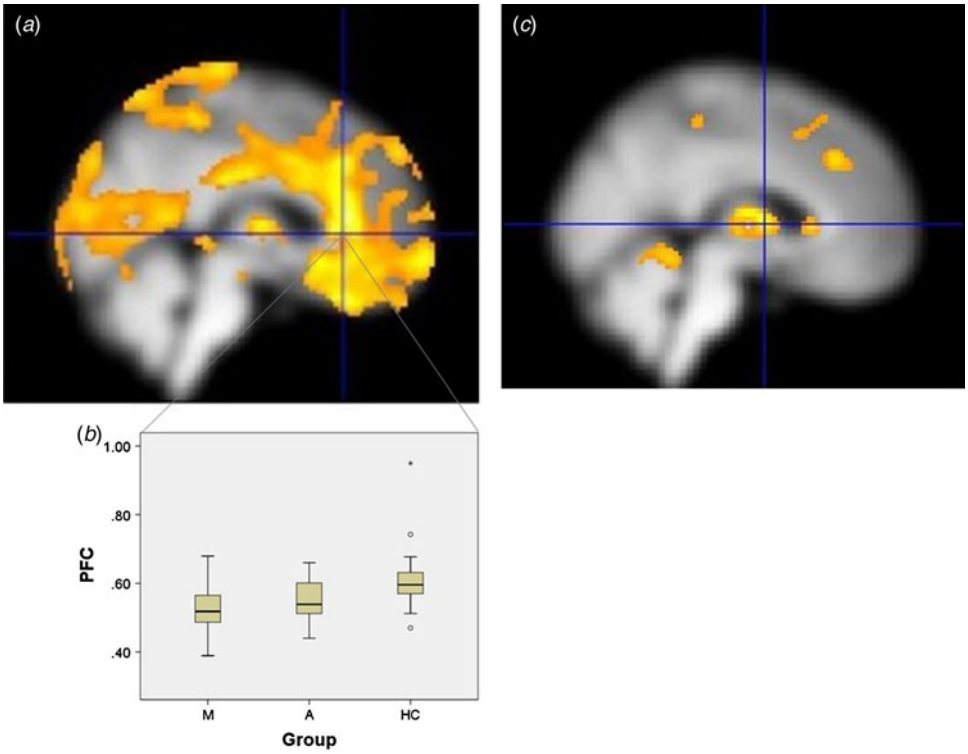

Fig. 2. Grey matter volume reductions. (*a*) Grey matter volume reductions in methadone maintenance treatment (MMT) patients relative to controls. Regions are significant ($p < 0.01$ whole-brain corrected level). (*b*) MMT patient (M), abstinent patient (A) and healthy control (HC) subgroups within the prefrontal cortex (PFC) (Montreal Neurological Institute coordinates −2, 34, 18). The central lines are medians; the boxes represent interquartile ranges; the whiskers represent ranges; circles outliers; the asterisk is an extreme outlier. Median value of the MMT group was significantly different ($p < 0.01$) from those of the abstinent and control groups. (*c*) Grey matter volume reductions in abstinent patients relative to controls. Regions are significant ($p < 0.01$ whole-brain corrected level).

Table 3. *Between-group comparisons*[a]

	x	y	z	*z* Value
Methadone group				
Anterior cingulate	−2	34	16	4.1
Orbitofrontal cortex	18	54	0	4.0
Caudate nucleus	−18	12	12	4.6
Globus pallidus	10	10	2	3.3
Nucleus accumbens	−6	10	10	4.1
Insula	34	−6	16	3.6
Occipital cortex	14	−98	−24	4.4
Abstinent group				
Thalamus	−2	−6	10	3.93
Midbrain	2	30	36	3.47

Grey matter reduction in methadone patients and abstinent patients in comparison with controls. Coordinates (x, y, z) reported in Montreal Neurological Institute space. All results significant at $p < 0.01$, cluster extent corrected across the whole brain.

different stages of the treatment programme (stable MMT *v.* abstinence in former MMT patients). We also tested for differences in cognitive impulsivity and non-planning impulsivity comparing MMT, ABS and healthy control groups. Stable MMT participants deliberated longer and placed higher bets earlier on the CGT and showed impaired strategic planning compared with healthy controls. ABS participants showed impairment in quality of decision-making, delay aversion and risk adjustment on the CGT and non-planning impulsivity compared with healthy controls. MMT participants had widespread grey matter reductions in the orbitomedial prefrontal cortex, caudate, putamen and globus pallidus. In contrast, ABS participants showed midbrain-thalamic grey matter reductions. The behavioural abnormalities correlate with structural grey matter abnormalities, providing evidence that the ABS group represent an intermediate group, with regard to behavioural abnormalities and brain structure abnormalities, between MMT participants and healthy controls.

Several studies have suggested impairment in cognitive impulsivity and non-planning impulsivity in opioid dependence (Ersche *et al.* 2005; Baldacchino *et al.* 2015). However, these studies did not address the

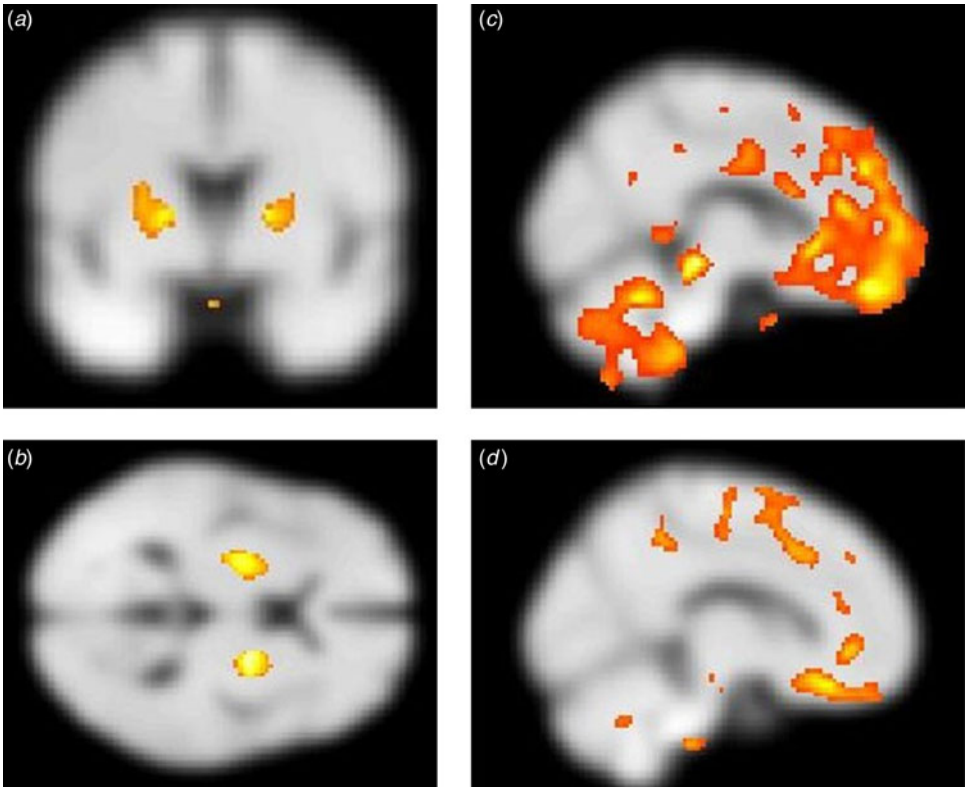

Fig. 3. Grey matter volume and methadone maintenance treatment (MMT). (*a*) Grey matter reductions in the bilateral globus pallidus in MMT patients correlating with stable methadone dose. (*b*) Grey matter reductions in the bilateral globus pallidus in MMT patients correlating with Cambridge Gambling Task (CGT) risk adjustment scores. (*c*) Grey matter reductions in the orbito-medial prefrontal cortex correlating with CGT risk-taking scores. (*d*) Grey matter volume reductions in the rostral prefrontal cortex correlating with mean subsequent five moves from Stockings of Cambridge.

issue of possible long-lasting changes as a result of chronic opioid use, and not address the issue of possible reversibility with abstinence. Our findings provide evidence that cognitive processes that are particularly associated with the prefrontal cortex are disrupted during chronic opioid use, but not during abstinence. MMT patients differed from healthy controls in that they took longer to make decisions during the CGT. However, the ABS group differed in delay aversion outcomes for cognitive impulsivity. It is possible that these changes are related to opioid dependence or the effects of subacute opioid withdrawal.

Our results show that MMT patients exhibited grey matter reductions in the orbito-medial prefrontal cortex, bilateral caudate nucleus and globus pallidus. Notably, the orbito-medial prefrontal cortex is implicated in processing drug-related information in addiction (Volkow *et al.* 1997; Volkow & Fowler, 2000) and the dorsal caudate in compulsive drug seeking and habit formation (Everitt *et al.* 2008; Koob & Volkow, 2010). Abnormally reduced frontal cortex activity has been linked with a reduction in dopamine striatal D_2 receptor availability (Volkow *et al.* 1997). Consistent with the latter, increased cognitive impulsivity correlated with grey matter reductions in the orbito-medial prefrontal cortex, but did not similarly correlate in the ABS group. This suggests that orbitofrontal cortex abnormalities are not linked to opioid exposure and may, alternatively, be linked to vulnerability to develop drug dependence (Adinoff *et al.* 2001), or an effect of non-opioid drug exposure prior to MMT (Volkow *et al.* 2011). Consistent with the latter interpretation, orbitofrontal grey matter reductions have been reported to be associated with increased risk taking in cocaine-, amphetamine- and alcohol-dependent individuals, using the Iowa Gambling Task (Tanabe *et al.* 2009). In animal studies, there is evidence that morphine administration increases impulsivity (Pattij *et al.* 2009) which normalizes when administration is stopped (Harvey-Lewis *et al.* 2012). In the present study, a negative correlation between methadone dose and CGT risk adjustment was present. This is consistent with animal studies reporting pallidal changes as a result of chronic opioid use (Gurwell *et al.* 2001). As reported decades ago, bilateral gross symmetric lesions of the globus pallidus were attributable to heroin intoxication (Strassmann *et al.* 1969) and subsequently more subtle lesions were observed in

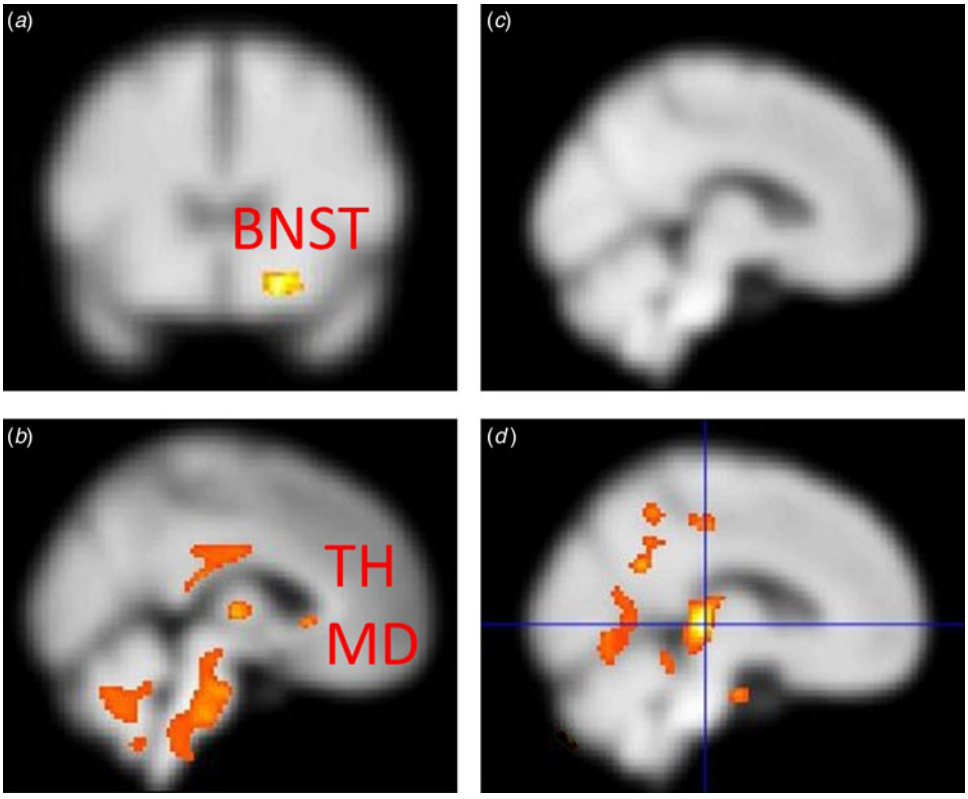

Fig. 4. Grey matter volume and abstinent (ABS) patients. (*a, b*) Grey matter reductions in the bed nucleus of the stria terminalis (BNST), thalamus (TH) and midbrain (MD) in ABS patients correlating with the last stable methadone dose. (*c*) No grey matter reductions in the ABS group correlating with Cambridge Gambling Task risk taking. (*d*) Grey matter reductions in the putamen and BNST in ABS patients correlating with mean subsequent five moves from Stockings of Cambridge.

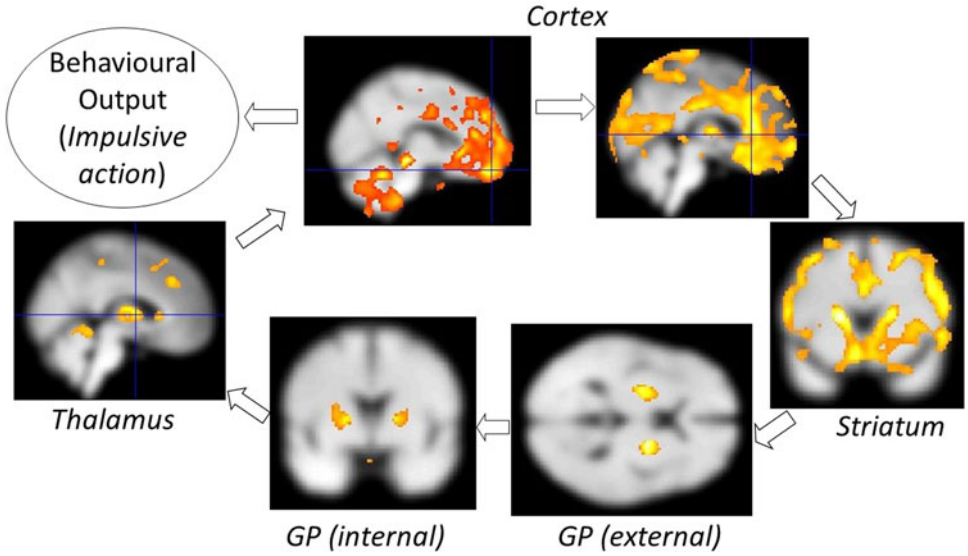

Fig. 5. Summary. Brain abnormalities summarized according to the cortico-basal ganglia-thalamocortical loop. This circuit originates from grey matter volume reductions in methadone maintenance treatment and abstinent patients significantly explained by opioid exposure (stable methadone dose, last stable methadone dose) and behavioural measures (Cambridge Gambling Task and Stockings of Cambridge). GP, Globus pallidus.

Table 4. *Summary of the cognitive and neuroimaging outcomes*

Cognitive domain	Test	Methadone group	Abstinent group
Cognitive impulsivity	CGT	Quality of decision making, deliberation time, risk adjustment ↓ Bilateral globus pallidus, ↓ orbito-medial prefrontal cortex	Quality of decision making, delay aversion, risk adjustment ↓ Periaqueductual grey, ↓ thalamus
Non-planning impulsivity	SOC	Problems solved in minimum moves, problems solved in five moves, mean subsequent thinking time five moves, mean subsequent thinking time five moves ↓ Orbito-medial prefrontal cortex, ↓ putamen, ↓ rostromedial prefrontal cortex	Problems solved in minimum moves, problems solved in five moves, mean subsequent thinking time five moves, mean subsequent thinking time five moves ↓ Putamen, ↓ bed nucleus of stria terminalis

CGT, Cambridge Gambling Task; ↓, reductions in grey matter; SOC, Stockings of Cambridge.

Table 5. *Logistic regression model*[a]

Predictor	EXP (B)	*p*
Frequency of use		
Number of years dependent on heroin	0.04	0.024
Withdrawal exposure		
Number of previous detoxifications (opioid)	1.3	N.S.
Number of previous detoxifications (alcohol)	2.5	N.S.
Treatment		
Initial titration of methadone dose (index)	0.483	0.01
Stable methadone dose (mg)	0.483	0.002
Days receiving methadone treatment	−0.511	0.03

N.S., Not significant.

[a] Results of the binary logistic regression model with exponential (β) = EXP(B), using as the response at the treatment outcome for the methadone group and abstinent group.

5–10% of heroin addicts at post-mortem (Andersen & Skullerud, 1999). As with motor impairments as a consequence of globus pallidus lesions (Andersen & Skullerud, 1999), neuropsychological impairments may depend on which part of the globus pallidus that has been damaged. Furthermore, it has been reported that hypoventilation caused by opioid use with paradoxical vasoconstriction results in bilateral, symmetrical infarcts of the globus pallidus (Daras *et al.* 2001). Notably, sleep apnoea (Egan *et al.* 2005) has been reported to occur in 30% of patients receiving MMT (Wang & Teichtahl, 2007). The incidence of sleep apnoea and ataxic breathing correlates with plasma methadone levels (Wang *et al.* 2005) and opioid dose (Walker *et al.* 2007). Consequently, there may be a link between higher doses of methadone, sleep apnoea and globus pallidus grey matter reductions. However, it has been reported that changes observed in MRI may be related to shifts in water content from and to glia cells because of the effects of steroid hormones or cytokines (Lucassen *et al.* 2014). This could be linked to stress responses due to short-term abstinence (6 months) or as a result of methadone intake.

Abstinent patients exhibited grey matter reductions in the thalamus and midbrain consistent with a previous study (Williams *et al.* 2007). Our study also found grey matter reductions in the BNST associated with increased LSMD. The BNST is a powerful modulator of addictive behaviour, with a major input from noradrenergic innervation and is a dense centre of neurones expressing corticotropin-releasing factor with cell bodies and terminals which could also be linked with impairment in cognitive impulsivity and non-planning impulsivity (Koob & Volkow, 2010). The reduction in the BNST may be specific to the abstinent group because it is involved in stress responses or it could be associated with decreased stress in recovery. Deep brain stimulation has been attempted previously in the BNST in patients and there is some evidence for drug dependence reduction (Langevin, 2012). Consistent with this, we found that grey matter volume reductions in thalamus and midbrain grey matter correlated negatively with measures of impaired cognitive impulsivity and non-planning impulsivity.

In conclusion, as hypothesized, MMT maintained patients exhibited abnormal behaviour linked to abnormal brain structure, and behavioural and brain abnormalities were least in ABS patients. However the extent to which these differences reflect a coincidence of MMT cessation or factors present during MMT promoting cessation remain unclear. We therefore suggest that a longitudinal study is required to determine whether abstinence improves abnormalities, or patients who achieve abstinence have reduced abnormalities before methadone cessation.

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